

## CPD

# Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking

**S. A. Walsh and D. Creamer***Department of Dermatology, King's College Hospital, Denmark Hill, London, UK*

doi:10.1111/j.1365-2230.2010.03967.x

**Summary**

Drug reaction with eosinophilia and systemic symptoms (DRESS) describes a severe medication-induced adverse reaction, which has cutaneous, haematological and solid-organ features. It is one of the triad of life-threatening drug hypersensitivity dermatoses, along with acute generalized exanthematous pustulosis (AGEP) and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). In this article, we discuss several controversies that surround DRESS, including problems with nomenclature and the lack of consensus in diagnostic criteria.

**DRESS: an evolving nomenclature**

Drug reaction with eosinophilia and systemic symptoms (DRESS) is just one of several synonymous terms used to describe a severe, idiosyncratic reaction to a drug, which characteristically arises after a long latency period (time between introduction of culprit medicine and onset of the reaction). All the names used refer to a disease, clinically distinct from the other SCAR syndromes (Severe Cutaneous Adverse Reactions) which presents with rash, haematological abnormalities and systemic illness.

The proliferation of names for a single condition reflects the difficulties in defining the disorder and in clarifying diagnostic criteria. An initial attempt to name this pattern of severe drug reaction was made after the introduction of the first anticonvulsant drugs, hydantoin and its derivatives, in the 1940s.<sup>2</sup> Early in the clinical use of these agents there were reports of reactions producing cutaneous and systemic upset in an unpredictable and dose-independent manner. Lymphadenopathy was a consistent finding, and lymph-node biopsies from affected patients were noted

to have a lymphomatous pathological appearance. In 1959, Saltztein collated a number of published reports with seven of his own cases, and proposed the term 'drug-induced pseudolymphoma' to describe this condition.<sup>3</sup> With the development of carbamazepine in the 1960s came reports of a syndrome similar to Saltztein's pseudolymphoma, but with rash and fever in addition to lymphadenopathy, and the term 'anticonvulsant hypersensitivity syndrome' (AHS) was introduced.<sup>4</sup> When it became apparent that other classes of drug such as sulfonamides, allopurinol and, more recently, antiretrovirals, could cause a similar constellation of symptoms, AHS was superseded by the term 'drug-induced hypersensitivity syndrome' (DIHS) or more simply 'hypersensitivity syndrome' (HSS).<sup>5</sup> In 1996, Callot *et al.*<sup>5</sup> reported a series of 24 patients with drug-induced dermatoses, the cases being divided into 3 who had no constitutional upset and a pseudolymphomatous pathology, and 21 with an acute systemic illness, an inflammatory pathology and a circulating eosinophilia. Cases of SJS/TEN and AGEP were excluded. Subsequently, a new term, 'drug rash with eosinophilia and systemic symptoms', was coined by Bocquet *et al.*<sup>6</sup> for the group with systemic upset. Although a dermatosis is usual in DRESS, the extent of skin involvement is variable and therefore the 'R' in DRESS was subsequently changed from 'rash' to 'reaction'. In 1998, the nomenclature was further confused by Sontheimer's suggestion of 'drug-induced delayed multiorgan

*Correspondence:* Dr Sarah A. Walsh, Department of Dermatology, Normanby Building, King's College Hospital, Denmark Hill, London, SE5 9RS, UK  
E-mail: sarahwalsh1@nhs.net

Conflict of interest: none declared.

Accepted for publication 20 August 2010

hypersensitivity syndrome' (DIDMOHS) to describe this disorder.<sup>7</sup>

As can be seen, the subject is littered with an array of names and acronyms: AHS, DIHS, HSS, DRESS and DIDMOHS. An up-to-date literature search will cite papers using all of these terms published in 2009 and 2010. Clearly, a consensus in terminology is essential to focus diagnostic and research efforts. RegiSCAR, the international study group dedicated to investigating such reactions, has adopted the term HSS/DRESS, which acknowledges elements of the pathogenesis (hypersensitivity), aetiology (drug) and clinical features (systemic symptoms).

## Clinical features

The broad spectrum of clinical features and long latency period in HSS/DRESS often results in diagnostic delay. Typically, patients present with fever, rash, lymphadenopathy, leucocytosis and abnormal liver tests which, understandably, may suggest an infectious illness. However assessment of the skin signs and haematological abnormalities should lead to a scrutiny of the patient's medication history and consideration of a drug hypersensitivity illness. Although a clinical overlap may exist with other severe drug eruption syndromes,<sup>1</sup> there is usually a clear constellation of features to implicate HSS/DRESS as a distinct disorder. Commonly, skin features are prominent, with an urticated, maculopapular eruption reported most often, but vesicles, bullae, pustules, cheilitis, purpura, target lesions and erythroderma have also been described.<sup>8,9</sup> Facial oedema, which is sometimes gross and mistaken for angio-oedema, is typical of HSS/DRESS. Although the eruption of DRESS is extensive and symptomatic, the major morbidity in DRESS arises from visceral involvement: fever (usually > 38 °C), lymphadenopathy, haematological abnormalities (most often eosinophilia) and involvement of at least one internal organ system (especially the liver, but also the kidneys, lungs and heart). Liver disturbance occurs in most cases with either hepatocellular or cholestatic damage, and in severe cases fulminant hepatic failure may necessitate liver transplantation. The mortality rate from DRESS has been estimated at 10%, most patients dying from liver failure.<sup>8,10</sup>

## Pathogenesis

The culprit drugs most commonly associated with DRESS are anticonvulsants, allopurinol, minocycline, sulfasalazine and abacavir.<sup>8,9</sup> Failure of drug detoxification pathways, leading to an accumulation of harmful

metabolites, has been hypothesized to explain anticonvulsant hypersensitivity.<sup>11</sup> Eosinophil activation and an inflammatory cascade may be induced by interleukin-5 release from drug-specific CD4+ and CD8+ T cells.<sup>12</sup> The observation of human herpesvirus (HHV) reactivation occurring during the acute phase of HSS/DRESS has led to suggestions of a pathogenic link. In longitudinal studies using PCR of viral DNA, Shiohara *et al.*<sup>13</sup> identified early reactivation of HHV6 and Epstein-Barr virus, with later involvement of HHV7 and cytomegalovirus. It has been proposed that in susceptible people, a transient drug-induced hypogammaglobulinaemia creates an immunological environment that permits viral reactivation.<sup>14,15</sup> The resulting expansion of virus-specific and nonspecific T cells is thought to mediate the clinical disease. The long latency period in HSS/DRESS has been explained by the time delay to viral reactivation, and the staggered appearance of the clinical features may reflect the sequential nature of reactivation.<sup>16</sup>

It is increasingly apparent that there is a genetic predisposition to adverse drug reactions. In particular, human leucocyte antigen-related genes have been identified as predictors for certain severe cutaneous adverse drug reactions syndromes. Studies have found that HLA-B\*1502 is associated with carbamazepine-induced SJS/TEN in some Asian populations, but the same association does not occur in HSS/DRESS.<sup>17-19</sup> However, a study of Han Chinese found that HLA-B\*5801 is a genetic marker for both SJS/TEN and HSS/DRESS caused by allopurinol.<sup>20</sup> It is hoped that further research may define pharmacogenetic disease-susceptibility markers to identify people at high risk of developing HSS/DRESS.

## Disease spectrum and diagnostic criteria

The considerable clinical heterogeneity in HSS/DRESS has hampered efforts to define a set of workable diagnostic criteria. The wide variability in clinical presentation was underlined in the largest major review, published in 2006, of cases presenting over a 15-year period in France.<sup>8</sup> In this series of 216 cases, fever, rash, lymphadenopathy, eosinophilia and liver dysfunction occurred commonly but were not a consistent feature in all cases. The only feature invariably present was a long latency period of 2–6 weeks. Cutaneous signs were present in most cases (> 70%); however, the pattern of skin involvement varied widely. Eosinophilia was the most common haematological abnormality, being present in > 50% of cases. Liver abnormalities emerged as the most frequent systemic symptom (> 60%).

The diverse presentations and varied organ involvement in HSS/DRESS highlight the need for a set of diagnostic criteria that are easily applicable in the clinical setting. The RegiSCAR group has suggested a series of criteria in which hospitalised patients with a drug rash must have at least three of four systemic features (fever, lymphadenopathy, internal organ involvement, haematological abnormalities) (Table 1).<sup>21</sup> The demonstration of systemic involvement is dependent on breaching threshold levels in haematological parameters (eosinophilia, atypical lymphocytosis) and biochemical tests (liver function, renal function). The strength of the RegiSCAR criteria lies in the selection of patients with a severe phenotype. Obvious disadvantages include the need for hospitalization and the measurement of atypical lymphocytes, which is not always readily available. Nonetheless, application of these criteria has been used successfully to validate HSS/DRESS cases at clinical meetings.

Another set of criteria for HSS/DRESS, generated by a Japanese group, has included HHV6 activation as a diagnostic feature (Table 2).<sup>22</sup> Although an association with HHV6 is of interest, definite confirmation that herpesviruses are central to the hypersensitivity reaction is currently lacking. An ambiguous role for virus reactivation coupled with low availability of the relevant assay reduces the worth of HHV6 as a diagnostic criterion.

Application of current diagnostic criteria excludes patients presenting with a drug-induced exanthem and systemic features, which are not sufficiently severe to qualify for a diagnosis of HSS/DRESS. This highlights the notion that HSS/DRESS exists as part of a disease spectrum, with patients at the mild end developing minor internal organ disturbance accompanying a drug-induced exanthem, whereas patients with the full-blown disease develop potentially life-threatening organ dysfunction or organ failure. Study of this lesser

**Table 1** Inclusion criteria for potential cases of drug reaction with eosinophilia and systemic symptoms published by RegiSCAR.<sup>21</sup>

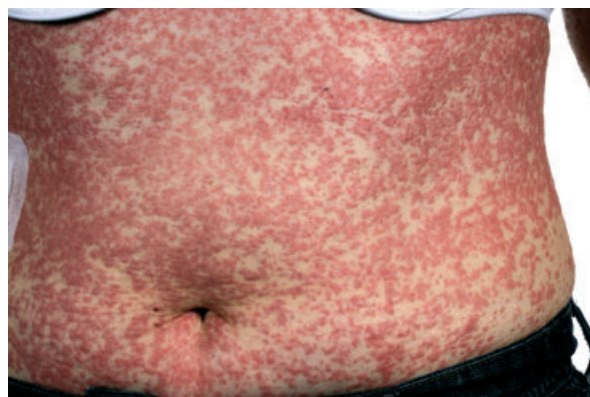
|   |
|---|
| Hospitalization                                 |
| Reaction suspected to be drug-related           |
| Acute rash                                      |
| Fever > 38 °C*                                  |
| Enlarged lymph nodes at a minimum of two sites* |
| Involvement of at least one internal organ*     |
| Blood count abnormalities*                      |
| Lymphocytes above or below normal limits        |
| Eosinophils above the laboratory limits         |
| Platelets below the laboratory limits           |

\*Three of these four criteria are required for diagnosis.

**Table 2** Diagnostic criteria for drug-induced hypersensitivity syndrome (DIHS) established by a Japanese consensus group.<sup>22</sup>

|   |
|---|
| Maculopapular rash developing > 3 weeks after starting with the suspected drug  |
| Prolonged clinical symptoms 2 weeks after discontinuation of the suspected drug |
| Fever (> 38 °C)   |
| Liver abnormalities (alanine aminotransferase > 100 U/L)*                       |
| Leucocyte abnormalities   |
| Leucocytosis (> $11 \times 10^9/L$ )  |
| Atypical lymphocytosis (> 5%)   |
| Eosinophilia (> $1.5 \times 10^9/L$ )   |
| Lymphadenopathy   |
| Human herpesvirus 6 reactivation  |

The diagnosis is confirmed by the presence of the seven criteria (typical DIHS) or of the first five criteria (atypical DIHS). \*This can be replaced by other organ involvement such as renal involvement.



**Figure 1** Maculopapular exanthematous eruption on the abdomen in a patient with drug reaction with eosinophilia and systemic symptoms following administration of trimethoprim for acne.

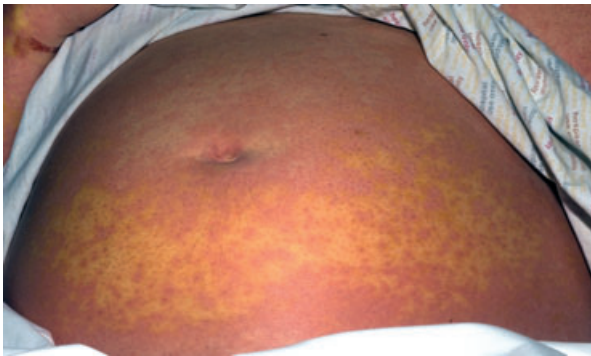


**Figure 2** Infiltration and oedema of the forehead, characteristic of patients with drug reaction with eosinophilia and systemic symptoms after treatment with minocycline for acne.





**Figure 3** Urticated plaques on the back of a patient with drug reaction with eosinophilia and systemic symptoms following administration of allopurinol.



**Figure 4** Presence of jaundice and ascites secondary to liver involvement in drug reaction with eosinophilia and systemic symptoms, as well as a rash.

form of HSS/DRESS ('mini-DRESS') may yield important information about interindividual variation in the expression of the clinical phenotype.

## Conclusion

As well as problems with disease definition and diagnostic criteria, a full understanding of HSS/DRESS

pathogenesis is currently lacking. Therapeutic trials can be planned only when agreements have been reached on diagnostic criteria and there is a more detailed appreciation of critical disease pathways.

At present, HSS/DRESS is generally treated with moderate- or high-dose oral corticosteroids, but response may be suboptimal and can result in a prolonged exposure to systemic glucocorticoid.<sup>9</sup> Other immunosuppressant agents, such as ciclosporin, are sometimes required.<sup>23,24</sup> The variation in outcome, ranging from modest systemic upset to death, highlights the need for a clinical tool to define disease severity. Development of a scoring system or a validated set of prognostic markers, will aid stratification of patient cohorts for clinical trials and help identify patients benefiting from early intervention with potent treatment and rapid transfer to an intensive care unit.

To improve both basic investigative research and clinical studies in HSS/DRESS an analysis of numerous validated cases and bio-banking of relevant samples is needed. A similar research effort in SJS/TEN has, over the past 20 years, yielded significant improvements in our comprehension of disease mechanisms, clinical patterns and therapeutic strategies.<sup>25,26</sup> Addressing the numerous unanswered questions in HSS/DRESS will only be achieved by collaborative research driven by clinical networks dedicated to the study of drug-induced illnesses and the SCAR syndromes.

## Learning points

- DRESS is but one term of many used to describe an idiosyncratic, systemic reaction to a medicine.
- Confusion about the nomenclature has hampered collation of experience with this disease.
- It is likely that susceptibility to DRESS is governed by both genetic and acquired factors.
- DRESS represents a spectrum of disease from a clinically mild presentation, characterized by rash, transient eosinophilia and lymphadenopathy, to a fulminating, severe presentation with marked derangement of organ function.
- Currently DRESS is treated with oral corticosteroids; however optimum treatment for DRESS remains unclear, and further collation of data in international registries represents the best means of elucidating answers to therapeutic questions.

## References

- Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Eng J Med* 1994; **331**: 1272–85.
- Coope R, Burrows R. Treatment of epilepsy with sodium diphenyl hydantoin. *Lancet* 1940; **1**: 490–2.
- Saltzstein S, Ackerman L. Lymphadenopathy induced by anticonvulsant drugs and mimicking clinically and pathologically malignant lymphomas. *Cancer* 1959; **12**: 164–82.
- Vittorio C, Muglia J. Anticonvulsant hypersensitivity syndrome. *Arch Intern Med* 1995; **155**: 2285–90.
- Callot V, Roujeau JC, Bagot M *et al*. Drug-induced pseudolymphoma and hypersensitivity syndrome. Two different clinical entities. *Arch Dermatol* 1996; **132**: 1315–21.
- Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms (DRESS)). *Semin Cutan Med Surg* 1996; **15**: 250–7.
- Sontheimer RD, Houghton KR. DIDMOHS: a proposed consensus nomenclature for the drug-induced delayed multi-organ hypersensitivity syndrome. *Arch Dermatol* 1998; **134**: 874–6.
- Peyriere H, Dereure O, Breton H *et al*. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2006; **155**: 422–8.
- Eshki M, Allanore L, Musette P *et al*. Twelve year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 2009; **145**: 67–72.
- Proudfoot LE, Watson K, Higgins EM, Creamer D. Twenty cases of DRESS syndrome: culprits, clinical features, treatment and outcome. *Br J Dermatol* 2009; **161** (Suppl. 1): 5.
- Shear N, Spielberg S, Grant D. Differences in metabolism of sulphonamides predisposing to idiosyncratic toxicity. *Ann Intern Med* 1986; **105**: 179–84.
- Choquet-Kastylevsky G, Intrator L, Chenal C *et al*. Increased levels of IL5 are associated with generation of eosinophilia in drug-induced hypersensitivity syndrome. *Br J Dermatol* 1998; **139**: 1026–32.
- Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS). A reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. *Allergol Int* 2006; **55**: 1–8.
- Aihara Y, Ito SI, Kobayashi Y *et al*. Carbamazepine-induced hypogammaglobulinaemia and reactivation of human herpesvirus 6 infection demonstrated by real-time quantitative polymerase chain reaction. *Br J Dermatol* 2003; **149**: 165–9.
- Kano Y, Inaoka M, Shiohara T. Association between human herpesvirus 6 reactivation and hypogammaglobulinaemia. *Arch Dermatol* 2004; **140**: 183–8.
- Kano Y, Hiraharas K, Sakuma K, Shiohara T. Several herpesviruses can reactivate in a severe drug-induced multi-organ reaction in the same sequential order as graft-versus-host disease. *Br J Dermatol* 2006; **155**: 301–6.
- Mehta TY, Prajapati LM, Mittal B *et al*. Association of HLA-B\*1502 allele and carbamazepine-induced Stevens-Johnson syndrome among Indians. *Indian J Dermatol Venereol Leprol* 2009; **75**: 579–82.
- Man CB, Kwan P, Baum L *et al*. Association between HLA-B\*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia* 2007; **48**: 1015–18.
- Yang CW, Hung SI, Juo CG *et al*. HLA-B\*1502-bound peptides: implications for the pathogenesis of carbamazepine-induced Stevens-Johnson syndrome. *J Allergy Clin Immunol* 2007; **120**: 870–7.
- Hung SI, Chung WH, Liou LB *et al*. HLA-B\*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci U S A* 2005; **102**: 4134–9.
- Kardaun SH, Sidoroff A, Valeyrie-Allanore L *et al*. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Response Br J Dermatol* 2007; **156**: 609–10.
- Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. *Br J Dermatol* 2007; **156**: 1045–92.
- Zuliani E, Zwahlen H, Gilliet F. Vancomycin-induced hypersensitivity reaction with acute renal failure: resolution following cyclosporine treatment. *Clin Nephrol* 2005; **64**: 155–8.
- Harman KE, Morris SD, Higgins EM. Persistent anticonvulsant hypersensitivity syndrome responding to ciclosporin. *Clin Exp Dermatol* 2003; **28**: 364–5.
- Mockenhaupt M, Viboud C, Dunant A *et al*. Stevens Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR study. *J Invest Dermatol* 2008; **128**: 35–44.
- Bastuji-Garin S, Fouchard N, Bertocchi M *et al*. SCORTEN, a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol* 2000; **115**: 149–53.

## CPD questions

### Learning objective

The purpose of these questions is to demonstrate an up-to-date understanding of DRESS, including problems with nomenclature and diagnostic criteria.

#### Question 1

Which one of the following infective agents has been implicated in the pathogenesis of DRESS?

- a) Human herpesvirus (HHV)6
- b) Mycoplasma
- c) Prion disease
- d) Streptococcus
- e) Tuberculosis

#### Question 2

The following all form part of the diagnostic criteria for DRESS except:

- a) Bullae > 20 mm in diameter
- b) Deranged liver function: alanine aminotransferase (ALT) > 100 U/L
- c) Eosinophil count >  $1.5 \times 10^9/L$
- d) Fever > 38 °C
- e) Lymphadenopathy involving > 2 lymph-node basins

#### Question 3

Which one of the following features distinguishes DRESS from a drug-induced exanthem?

- a) Exposure to a potential culprit medication
- b) Latency of > 2 weeks between exposure to the drug and onset of symptoms
- c) Presence of a morbilliform rash
- d) Recurrence of the eruption on re-exposure to the causative drug
- e) Response to drug withdrawal and application of topical steroids

#### Question 4

Which one of the following organs is most commonly involved in DRESS?

- a) Brain
- b) Kidney
- c) Liver
- d) Pancreas
- e) Thyroid

#### Question 5

Which of the following treatments is indicated in severe DRESS?

- a) Activated protein C (APC)
- b) Intravenous immunoglobulin
- c) Dapsone
- d) Systemic corticosteroids
- e) Tetracycline antibiotics

## Instructions for answering questions

This learning activity is freely available online at [www.wileyblackwellcme.com](http://www.wileyblackwellcme.com).

Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
- Reflect on the article
- Register or login online at [www.wileyblackwellcme.com](http://www.wileyblackwellcme.com) and answer the CPD questions
- Complete the required evaluation component of the activity

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.